



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2008-N-0448]

International Drug Scheduling; Convention on Psychotropic Substances; World Health Organization Scheduling Recommendations for Gamma-hydroxybutyric Acid

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is providing interested persons with the opportunity to submit written comments and to request an informal public meeting concerning recommendations by the World Health Organization (WHO) to impose international manufacturing and distributing restrictions, under international treaties, on certain drug substances. The comments received in response to this notice and/or public meeting will be considered in preparing the U.S. position on these proposals for a meeting of the United Nations Commission on Narcotic Drugs (CND) in Vienna, Austria, in March 2013. This notice is issued under the Controlled Substances Act (the CSA).

DATES: Submit either electronic or written comments by [INSERT DATE 15 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Submit requests for a public meeting on or before [INSERT DATE 10 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. (For additional information, see also section IV of this document).

ADDRESSES: Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

James R. Hunter,
Center for Drug Evaluation and Research,
Controlled Substance Staff,
Food and Drug Administration,
Bldg. 51, rm. 5150,
10903 New Hampshire Ave.,
Silver Spring, MD 20993-0002,
301-796-3156,
email: james.hunter@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

The United States is a party to the 1971 Convention on Psychotropic Substances (the Convention). Section 201(d)(2)(B) of the CSA (21 U.S.C. 811(d)(2)(B)) provides that when the United States is notified under Article 2 of the Convention that CND proposes to decide whether to add a drug or other substance to one of the schedules of the Convention, transfer a drug or substance from one schedule to another, or delete it from the schedules, the Secretary of State must transmit notice of such information to the Secretary of Health and Human Services (Secretary of HHS). The Secretary of HHS must then publish a summary of such information in the Federal Register and provide opportunity for interested persons to submit comments. The Secretary of HHS must then evaluate the proposal and furnish a recommendation to the Secretary of State that shall be binding on the representative of the United States in discussions and negotiations relating to the proposal.

As detailed in the following paragraphs, the Secretary of State has received one notification from the Secretary-General of the United Nations (the Secretary-General) regarding substances to be considered for control under the Convention. This notification reflects the recommendation from the 35th WHO Expert Committee for Drug Dependence (ECDD), which met in June 2012. In the Federal Register of September 05, 2008 (73 FR 51823), FDA announced the WHO ECDD review and invited interested persons to submit information for WHO's consideration.

The full text of the notification from the Secretary-General is provided in section II of this document. Section 201(d)(2)(B) of the CSA requires the Secretary of HHS, after receiving a notification proposing scheduling, to publish a notice in the Federal Register to provide the opportunity for interested persons to submit information and comments on the proposed scheduling action.

II. United Nations Notification

The formal United Nations notification that identifies the drug substance and explains the basis for the recommendations is reproduced as follows:

Reference: NAR/CL.6/2012

WHO/ECDD35 1971C-Art.2

CU 2012/196/DTA/SGB

The Secretary-General of the United Nations presents his compliments to the Secretary of State of the United States of America and has the honour to inform the Government that the Director-General of the WHO, under article 2, paragraphs 1, 4, and 6, of the Convention on Psychotropic Substances of 1971 (1971 Convention), has notified the Secretary-General that it is

of the opinion that Gamma-hydroxybutyric acid (GHB) should be transferred from Schedule IV to Schedule II of the 1971 Convention.

In accordance with the provisions of article 2, paragraph 2, of the 1971 Convention, the Secretary-General hereby transmits the relevant excerpts of the notification as Annex I to the present note. Also in accordance with the same provisions, the notification from WHO will be brought to the attention of the CND at its next session in March 2013.

In connection with the notification, WHO has also submitted excerpts from the report of the Thirty-fifth session of the WHO ECDD (4-8 June 2012) which reviewed the substance. The excerpts from that report concerning GHB are hereby transmitted as Annex II. The excerpts are currently available in English only, pending receipt of the official French translation from the WHO. The report of the Thirty-fifth session of the WHO ECDD can be retrieved from the following Web site:

http://www.who.int/medicines/areas/quality_safety/35thecddmeet/en/index.html. (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the Federal Register).

Any action or decision taken by the Commission with respect to this notification, pursuant to article 2, paragraphs 5 and 6, of the 1971 Convention, will be communicated to States Parties in due course. Article 2, paragraphs 5 and 6, reads as follows:

“5. The Commission, taking into account the communication from the WHO, whose assessments shall be determinative as to medical and scientific matters, and bearing in mind the economic, social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule I, II, III or IV. The Commission may seek further information from the WHO or from other appropriate sources.

“6. If a notification under paragraph 1 relates to a substance already listed in one of the Schedules, the WHO shall communicate to the Commission its new findings, any new assessment of the substance it may make in accordance with

paragraph 4 and any new recommendations on control measures it may find appropriate in the light of that assessment. The Commission, taking into account the communication from the WHO as under paragraph 5 and bearing in mind the factors referred to in that paragraph, may decide to transfer the substance from one Schedule to another or to delete it from the Schedules.”

To assist the Commission in reaching a decision, it would be appreciated if the Government could communicate any economic, social, legal, administrative, or other factors that it considers relevant to the possible rescheduling under the 1971 Convention, of GHB, at the latest by 28 December 2012 to the Executive Director of the United Nations Office on Drugs and Crime, c/o Secretary, Commission on Narcotic Drugs, P.O. Box 500, 1400 Vienna, Austria, FAX: +43-1-26060-5885, email: sgb@unodc.org.

9 November 2012

NAR/CL.6/201

Annex I

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Annex I

Relevant excerpts of letter addressed to the Secretary-General of the United Nations by the
Director-General of the World Health Organization

“With reference to article 2 of the Convention on Psychotropic Substances (1971), article 2, paragraphs 1, 4 and 6, I am pleased to submit the recommendations of the WHO, concerning the international control of γ -hydroxybutyric acid (GHB). The recommendation is that GHB be rescheduled from Schedule IV to Schedule II of the 1971 Convention. The basis for this recommendation is set out in an extract from the Report of the ECDD, which advises on these issues, attached to this letter.”

Geneva, 22 October 2012

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Annex II

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Annex II

Extract From the 35th Report of the Expert Committee on Drug Dependence

Recommendation on Gamma-hydroxybutyric acid (GHB)

This section provides information in addition to the information presented in the report of the Thirty-fourth meeting. The Expert Committee discussed GHB in the context of Gamma-butyrolactone and 1,4-butanediol (1,4-BD), precursors of GHB, see sections 4.4 and 4.5.

Substance identification and pharmacodynamics.

Gamma-hydroxybutyric acid (GHB), also known as 4-hydroxybutanoic acid and sodium oxybate, is a naturally occurring substance found in low concentrations in mammalian tissues. It is considered to act by binding to GHB-specific receptors and Gamma-aminobutyric acid B (GABAB) receptors. At pharmacological doses, it acts as a central nervous system depressant.

Previous reviews.

GHB was pre-reviewed during the Thirty-first and Thirty-second meetings, held in 1998 and 2000, respectively. In 2001, GHB was placed in Schedule IV of the 1971 Convention by a decision of the CND. It was again pre-reviewed at the Thirty-fourth ECDD meeting in 2006 (1), at which time the Expert Committee recommended a new critical review to consider GHB's possible rescheduling.

Evidence on dependence potential.

The Expert Committee examined additional information from the updated critical review report and peer-review reports. The Expert Committee noted that there is compelling evidence

that dependence on GHB exists in humans and noted withdrawal syndromes and withdrawal seizures.

Actual abuse.

The Expert Committee noted that at present, GHB appears to be mainly used and abused in the United States of America, Europe and Australia. Most GHB used illicitly originates from clandestine manufacture.

In their discussions, the Expert Committee and advisers agreed on the narrow margin of safety of GHB. There have been numerous reports from Europe and the United States of accidental fatal and non-fatal overdoses where GHB was implicated, both when used alone and with other substances.

The Expert Committee also noted there have been reports of GHB being used to facilitate sexual assault.

Therapeutic usefulness.

GHB is used as a medicine in some countries on a small scale for various indications. GHB is not included in the WHO Model List of Essential Medicines.

Need for the substance for other purposes (e.g., industrial).

The Expert Committee acknowledged the use of GHB in the production of a wide variety of industrial polymers.

III. Discussion

Although WHO has made specific scheduling recommendations for each of the drug substances, the CND is not obliged to follow the WHO recommendations. Options available to the CND for substances considered for control under the Psychotropic Convention include: (1) Acceptance of the WHO recommendations; (2) acceptance of the recommendations to control,

but control the drug substance in a schedule other than that recommended; or (3) reject the recommendations entirely.

GHB is classified as a central nervous system depressant. In 2002, FDA approved a GHB-containing product, Xyrem, for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy under the regulations in 21 CFR part 314, subpart H (21 CFR 314.520). Xyrem was included on the list of products deemed to have in effect an approved Risk Evaluation and Mitigation Strategy (REMS) under section 505-1 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355-1) at the time of the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA). The REMS for Xyrem includes a medication guide and healthcare provider education brochure, mandatory patient and prescriber certification through enrollment, and restricted dispensing of the drug through a central pharmacy. Xyrem is controlled domestically in Schedule III of the CSA, while bulk GHB and all other material containing GHB are controlled in Schedule I. In addition, illicit use of Xyrem is subject to Schedule I penalties of the CSA. GHB is controlled internationally in Schedule IV of the Psychotropic Convention. The WHO ECDD pre-reviewed GHB at its Thirty-fourth meeting and recommended it for critical review at a future meeting. The WHO ECDD met in Hammamet, Tunisia, from 4-8 June 2012, critically reviewed GHB, and recommended that it be rescheduled from Schedule IV to Schedule II of the Convention on Psychotropic Substances.

IV. Submission of Comments and Opportunity for Public Meeting

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be

seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

FDA does not presently plan to hold a public meeting. If any person believes that, in addition to their written comments, a public meeting would contribute to the development of the U.S. position on the substances to be considered for control under the Psychotropic Convention, a request for a public meeting and the reasons for such a request should be sent to James R. Hunter (see FOR FURTHER INFORMATION CONTACT) on or before [INSERT DATE 10 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

The short time period for the submission of comments and requests for a public meeting is needed to ensure that HHS may, in a timely fashion, carry out the required action and be responsive to the United Nations.

Dated: February 1, 2013.

Leslie Kux,

Assistant Commissioner for Policy.